Cytomegalovirus disease in inflammatory bowel disease: epidemiology and disease characteristics in a large single-centre experience

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Abstract: BACKGROUND Patients with inflammatory bowel disease (IBD) show an increased risk of developing cytomegalovirus (CMV) disease because of immunosuppressive medication and malnutrition. Here, we aimed to investigate the prevalence and clinical characteristics of CMV disease in our cohort of IBD patients. PATIENTS AND METHODS We carried out a retrospective analysis of 1023 IBD patients treated at our IBD clinic at the University Hospital Zurich between 2007 and 2014. CMV disease was defined as a positive immunohistochemistry for CMV and 14 patients were identified. RESULTS The prevalence of CMV disease in our IBD cohort was 1.37%. Twelve patients had ulcerative colitis and two had Crohn's disease with colonic involvement. All patients who developed CMV disease received immunosuppressive medication or, as in one case, had HIV infection. The most used immunosuppressive medications were steroids and azathioprine. The most common therapeutic strategy was the consecutive use of ganciclovir and valganciclovir. Ten patients recovered and two were treatment refractory; among these, one required colectomy and two had a relapse. CONCLUSION CMV disease may influence the clinical course of IBD. There is probably an association between CMV disease and IBD-specific medication. Risk factors, epidemiology and therapeutic strategy need to be further investigated.

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Cytomegalovirus disease in inflammatory bowel disease: epidemiology and disease characteristics in a large single-centre experience

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Background Patients with inflammatory bowel disease (IBD) show an increased risk of developing cytomegalovirus (CMV) disease because of immunosuppressive medication and malnutrition. Here, we aimed to investigate the prevalence and clinical characteristics of CMV disease in our cohort of IBD patients.

Patients and methods We carried out a retrospective analysis of 1023 IBD patients treated at our IBD clinic at the University Hospital Zurich between 2007 and 2014. CMV disease was defined as a positive immunohistochemistry for CMV and 14 patients were identified.

Results The prevalence of CMV disease in our IBD cohort was 1.37%. Twelve patients had ulcerative colitis and two had Crohn's disease with colonic involvement. All patients who developed CMV disease received immunosuppressive medication or, as in one case, had HIV infection. The most used immunosuppressive medications were steroids and azathioprine. The most common therapeutic strategy was the consecutive use of ganciclovir and valganciclovir. Ten patients recovered and two were treatment refractory; among these, one required colectomy and two had a relapse.

Conclusion CMV disease may influence the clinical course of IBD. There is probably an association between CMV disease and IBD-specific medication. Risk factors, epidemiology and therapeutic strategy need to be further investigated. Eur J Gastroenterol Hepatol 28:1329–1334

Introduction

Cytomegalovirus (CMV) is a member of the herpes-virus family, causing a common and usually asymptomatic viral infection, occurring in 40–100% of adults. Despite a high prevalence of CMV in the general population, clinically significant CMV disease mainly occurs in immunocompromised patients [1]. It is important to distinguish CMV infection, where an individual is positive by PCR or serologic analysis, from CMV disease, such as CMV colitis or CMV retinitis, where the virus causes significant clinical symptoms [2].

Haematoxylin and eosin (H&E), immunohistochemistry (IHC) and tissue PCR are the methods of choice to determine the presence of CMV in colon tissue as they are likely to be more appropriate to evaluate CMV involvement in colitis than antigenaemia, IgM and leucocyte DNA PCR testing [3]. H&E staining typically shows enlarged cells with large eosinophilic inclusions. The presence of these cells indicates not only infection, but is associated with colitis that is poorly responsive to standard inflammatory bowel disease (IBD) therapy, providing a diagnostic tool for CMV disease, namely, CMV colitis [4]. H&E staining has a high specificity (92–100%), but its sensitivity is in the range of 10–87% [3]. IHC has a very good sensitivity (78–93%) and uses monoclonal antibodies to identify the CMV early antigen. The specificity ranges between 92 and 100% [4].

IHC is important in the routine evaluation of IBD patients with severe disease before proceeding with step-up medical treatment or even surgery [5]. The clinical significance of a positive PCR of colonic tissue without other histological signs of infection remains unclear. The presence of viral DNA without histological features is likely to represent low-level reactivation of latent CMV infection [3].

Data on the prevalence of CMV colitis complicating IBD are sparse and further investigations are necessary to draw conclusions. A recent review from 2015 reported that the actual data cannot provide clear answers, mainly because of selection bias and different diagnostic methods [6]. However, probably a higher prevalence of CMV in steroid-resistant patients exists, with a female preponderance [5].

Nevertheless, IBD patients are at an increased risk for active CMV disease [4]. This predisposition is likely because of immunosuppression, mainly as a result of

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immunosuppressive therapy and poor nutrition, possible impairment of natural killer function and CMV tropism for sites of inflammation [1,7]. A common question is whether CMV leads to the development of IBD or whether it only worsens disease severity. The first theory is an unlikely option, considering that CMV disease is rare in patients with mild to moderate ulcerative colitis (UC) and Crohn's disease (CD) [3]. Studies on CMV, UC and steroid-resistance showed considerable heterogeneity, but there is sufficient evidence to show that CMV disease increases the biological severity of colitis [2]. Some authors noted that patients with CMV had a higher mortality and colectomy rate [7]. Furthermore, it remains to be investigated in which cases a specific treatment is needed and which cases feature a spontaneous remission.

The aim of this study was to characterize patients with CMV disease as diagnosed by a positive IHC for CMV from a total of 1023 patients in our IBD clinic at the University Hospital Zurich.

Patients and methods

We retrospectively identified 14 patients from a cohort of 1023 patients from the IBD clinic at the University Hospital Zurich treated between 2007 and 2014, who had a positive IHC for CMV after their diagnosis of either UC or CD in the context of ongoing disease activity, except for one case, where CMV was found in the stomach. An initial screening of the cohort, where we searched for the term 'CMV' in the electronic medical records, limited the results to 311 patients. From this group, we selected only those patients who finally had a positive CMV IHC result and a positive diagnosis of UC or CD.

We collected the following data: age, sex, first diagnosis of IBD, Vienna classification, presence of complications (fistulae and stenosis), surgical interventions, degree of colon involvement for UC, IBD-specific therapy: use of steroids and other immunosuppressive therapy alone or in combination [e.g. corticosteroids, budesonide, purine analoga (azathioprine, 6-mercaptopurine), methotrexate, antitumour necrosis factor alpha inhibitors (adalimumab, infliximab, certolizumab pegol) and anti-integrin inhibitors as vedolizumab], CMV-specific data: time of positive CMV IHC, results of other diagnostic tests (IgG and IgM serology, blood PCR, biopsy PCR, faecal PCR and H&E staining), presence of CMV disease relapses, conditions of treatment (as an inpatient or an outpatient), immunosuppressive therapy at the time of positive CMV IHC and treatment outcome of CMV disease, in particular, recovery. The presence of CMV relapses was defined as a second positive CMV IHC testing after conclusion of therapy and improvement of symptoms. Recovery was determined either by hospital exit, stopping of antiviral medication or a negative IHC after a previous positive one.

In terms of the results of the PCR tests, we considered only those who had a relationship with a positive result of a IHC; therefore, we excluded tests performed more than 2 weeks before IHC and tests performed after or during CMV treatment. For the two cases with relapses, only data on the primary event are considered in the tables; the details on the second event are discussed separately in the results.

The patient information that was collected was anonymized and deidentified before analysis and for publication.

Institutional review board statement

The cohort study was approved by the local ethical committees (IRB approval number: EK-1755, approved on 1 March 2010 by the Cantonal Ethics Committee of the Canton Zürich, Switzerland).

Results

Prevalence of CMV disease and patients' characteristics

From our IBD cohort, 396 (38.7%) patients had UC, 601 (58.8%) had CD and 26 (2.5%) were IBD unclassified. In terms of sex, 536 (52.4%) patients were men and 487 (47.6%) were women. From the 1023 patients, only 14 were diagnosed with a CMV-positive IHC between 2007 and 2014.

This contributed towards a prevalence of 1.37%. Of the entire cohort, of the 14 patients with a positive CMV IHC, 12 had CMV colitis, one had CMV proctitis and one had detectable CMV in the stomach. This case was described as a chronic and generalized CMV infection including a history of CMV pneumonia; in our study, it was classified as refractory to therapy.

General disease characteristics and demographic data of the patients are summarized in Table 1. Of the 14 patients, five were women and nine were men. A higher proportion of the patients had UC and only two had CD. The average age at the diagnosis of IBD was 36 years, with little differences between CD (32 years) and UC (37 years). The average age of the patients was 39 years at the time of positive IHC. One of the two patients with CD had fistulizing disease without luminal stenosis. Two out of the 12 patients with UC had undergone IBD-related surgery, seven had pancolitis, four had a left-sided colitis and one had proctitis. Thirteen of 14 patients had received immunosuppressive therapy. One patient did not receive any IBD-specific therapy because at the time of positive IHC, the diagnosis of UC was not provided; nonetheless, the clinical symptoms were already present. The diagnosis of UC was made histologically 3 months after CMV infection

Table 1. Patient and disease characteristics

Patient and disease characteristics	Total	CD	UC
Number	14	2	12
Female	5	1	4
Male	9	1	8
Average age at first diagnosis of IBD (years)	35.71	32	36.33
Average age at first positive IHC (years)	39.07	38	39.25
Fistulizing disease	1	1	
Stenosis	0	0	
History of surgery	2	0	2
Immunosuppressive therapy	13	2	11
Colitis disease extent	12		12
Pancolits	7		7
Left-sided colits	4		4
Proctitis	1		1
Treatment setting	14	2	12
Inpatients	11	2	9
Outpatients	3	0	3

CD, Crohn's disease; IBD, inflammatory bowel disease; IHC, immunohistochemistry; UC, ulcerative colitis.

after colitis reoccurred and recurrent CMV infection could be ruled out. The diagnosis emerged later, but it explained the patient's previous problems. Nevertheless, the patient was immunocompromised because of HIV infection.

Diagnostic tests for CMV detection

The results of all the diagnostic tests for CMV are presented in Table 2. All the patients included in the study had a positive IHC for CMV as the diagnostic criterion on which the diagnosis was finally based; here, we also describe the results of additional diagnostic tests that were performed. H&E staining showed positive results in eight out of 14 patients who performed the test. Faecal PCR was only performed in two patients, with positive results in both. Biopsy PCR was tested in seven patients and was always positive. Blood PCR was also tested in seven cases, showing positivity in five patients; blood PCR was performed on EDTA blood or citrate blood. Serology (enzyme-linked immunosorbent assay) for IgM and IgG was obtained in four patients, providing a positive result for IgG in all cases, but interestingly, only for one patient for IgM, probably reflecting a primoinfection or a reactivation.

All IHC-positive biopsies for CMV were obtained from inflamed mucosa. The average number of biopsies that was taken was 8 (2–24 biopsies). In three cases where IHC for CMV from inflamed mucosa was positive, biopsies from noninflamed mucosa were also taken, which were all IHC negative for CMV. In all patients, the CMV diagnosis was made after the diagnosis of IBD. In six patients, the diagnosis of CMV was made under treatment with azathioprine (Table 3).

IBD treatment

Medications at the time of positive IHC are shown in Table 3. In six patients, the CMV diagnosis was made under treatment with azathioprine (Table 3). In three cases, CMV diagnosis was made in patients who had a personal history of azathioprine therapy (>1 year after azathioprine therapy in two patients and duration unknown in one patient). The two most common medications at the time of positive IHC were steroids and azathioprine. Less common medications were infliximab and budesonide; adalimumab and 6-mercaptopurine were only used by two different patients. Azathioprine combined with steroids and infliximab with steroids were the two most common combinations of medications, used in three patients each. Steroids alone and the combination of azathioprine, budesonide and steroids each accounted for the therapy of two patients. Ten patients took mesalazine at the time of positive CMV IHC.

Table 3. IBD-specific medication taken at the time of positive CMV IHC

Medication at the time of CMV-positive IHC	Total	CD	UC
Number	14	2	12
Steroids	13	2	11
Azathioprine	6	2	4
Budenoside	3	1	2
Infliximab	4	0	4
Adalimumab	1	1	0
6-MP	1	0	1
Combinations of medication/single therapies	14	2	12
Azathioprine and steroids	3	0	3
Infliximab and steroids	3	0	3
Azathioprine, steroids and budenoside	2	1	1
Steroids	2	0	2
Azathioprine, steroids and adalimumab	1	1	0
Infliximab, steroids and 6-MP	1	0	1
Budenoside	1	0	1
No IBD-specific treatment	1	0	1

CD, Crohn's disease; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IHC, immunohistochemistry; 6-MP, 6-mercaptopurine; UC, ulcerative colitis.

Treatment and course of CMV disease

Data on CMV-specific therapy are summarized in Table 4. Most patients were treated consecutively with intravenous ganciclovir, followed by oral valganciclovir, four patients were treated only with oral valganciclovir (three of them were treated as outpatients) and two patients were treated only with intravenous ganciclovir. The standard intravenous ganciclovir dose was 5 mg/kg bodyweight every 12 h and the oral valganciclovir dose was 900 mg 2× daily, or adopted to kidney function if necessary.

Details on therapy outcome are shown in Fig. 1. Six out of eight patients treated with intravenous ganciclovir, followed by oral valganciclovir showed remission, one patient developed a relapse and one patient was therapy refractory. One of the patients treated only with intravenous ganciclovir developed a relapse; the other required a total colectomy with ileostomy. All four patients treated with valganciclovir achieved recovery.

Eleven patients were primarily treated as inpatients and the other three as outpatients (all treated with valganciclovir). Ten patients recovered from disease, two were therapy refractory, one of these patients requiring colectomy, and two developed a relapse. One of the two therapy-refractory patients had CD and had a chronic and generalized CMV infection treated primarily with ganciclovir, followed by a long-term valganciclovir regimen; however, it must be noted that this patient was not tested for CMV colitis, but the virus was found in the stomach.

Table 2. Diagnostic methods for CMV

Diagnostic methods	Positive tests/total of tests performed	CD	UC
IHC	14/14	2/2	12/12
Histology (H&E)	8/14	1/2	7/12
Faecal PCR	2/2		2/2
Biopsy PCR	7/7		7/7
Blood PCR	5/7	1/1	4/6
IgG serology	4/4		4/4
IgM serology	1/4		1/4

CD, Crohn's disease; CMV, cytomegalovirus; H&E, haematoxylin and eosin; IHC, immunohistochemistry; UC, ulcerative colitis.

Table 4. Treatment outcome and antiviral medication

Treatment outcome and antiviral medication	Total	CD	UC
Total	14	2	12
Ganciclovir	2	0	2
Valganciclovir	4	0	3
Ganciclovir and valganciclovir	8	2	6
Recovery	10	1	9
Relapse	2	0	2
Therapy refractory	1	1	0
Therapy refractory and colectomy	1	0	1

CD, Crohn's disease; UC, ulcerative colitis.

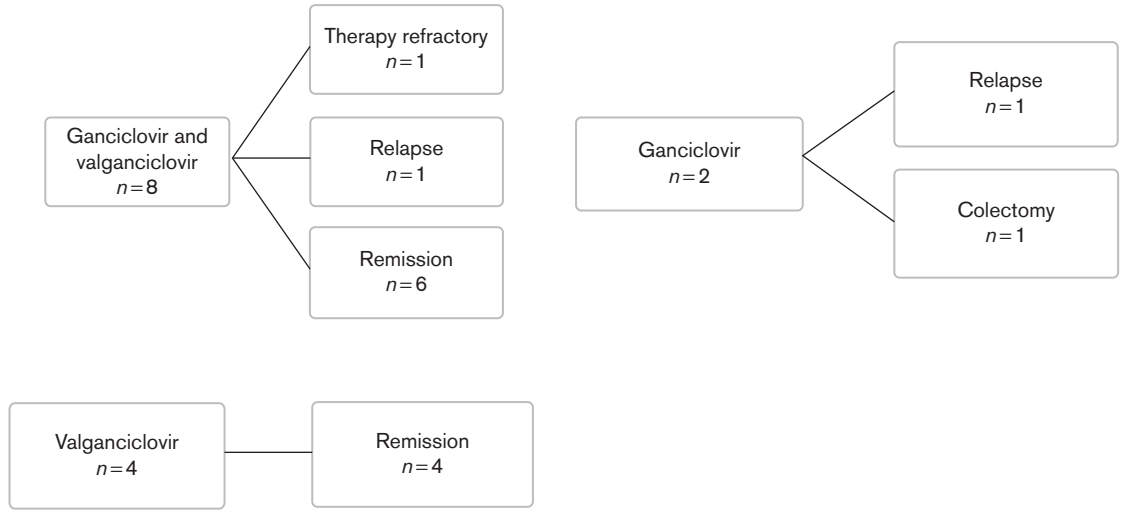

Fig. 1. Details on treatment outcome.

The other patient, who had UC, presented to the hospital for a steroid-refractory flare and was treated with ganciclovir without a positive effect on the symptoms, and then required a colectomy.

Relapses

Overall, two UC patients out of 14 IBD patients developed relapses, defined as a second positive IHC after the completion of antiviral therapy and improvement of symptoms. The interval between the two positive IHC was 241 and 91 days, respectively. One patient was treated the first time with ganciclovir, showing an improvement in the clinical symptoms and general conditions; the relapse was treated with ganciclovir and valganciclovir. The other patient was treated primarily with ganciclovir and valganciclovir, achieving an improvement of the clinical course; the relapse resolved spontaneously and no antiviral treatment was required.

Discussion

In our retrospective analysis of CMV disease, we found a prevalence of 1.37%; the most commonly used medications at the time of positive CMV IHC were the steroids azathioprine and infliximab. Most patients were treated with both intravenous ganciclovir and oral valganciclovir.

The prevalence of CMV disease varies markedly between UC and CD [8]. Studies on patients with inactive or mild–moderate UC did not show an increased risk of CMV colitis, diagnosed with H&E and IHC. The most extensive literature exists on severe and/or steroid-refractory UC, terms that are used interchangeably and are not clearly defined. Therefore, findings are difficult to interpret [8]. The prevalence of CMV diagnosed with HE or IHC varies considerably even between the UC patients, ranging from 0.5% in severe steroid-resistant colitis to 3% in severe colitis. The highest values were found in patients who needed an urgent colectomy, where the prevalence ranged between 11.5 and 27% [8].

Nevertheless, histological prevalence (H&E or IHC) of CMV in UC patients has been reported to be between 4.5 and 13.8% according to another systematic review [6]. The large heterogeneity of the results can be explained mainly by selection bias and heterogeneity in diagnostic methods [6]. Even if seropositivity in CD patients is as high as in other populations, CMV disease is rare in these patients. CMV disease diagnosed by IHC was not detected in most studies in CD patients [8].

The somewhat low prevalence of 1.37% in our large single-centre IBD cohort might be attributed to the fact that we included both UC and CD patients of our cohort, calculating the prevalence on a population composed not only of patients with severe or therapy-refractory diseases but including every IBD patient treated in our tertiary centre between 2007 and 2014. However, for daily practice, this also means that CMV prevalence overall is rather small, even in a tertiary referral centre. Some theories attempt to explain the differences in CMV disease prevalence between UC and CD [9]; however, these results were obtained from small studies and should be interpreted with caution [8]. One explanation suggests that in IBD patients, tumour necrosis factor could be associated with CMV infection or reactivation. In contrast to tumour necrosis factor, interferon-γ (IFNγ), which is produced from CD4 + T-cells, could suppress CMV reactivation. CD is considered a Th1-type inflammatory process with high expression of IFNγ. Therefore, the differences in inflammatory mechanisms could explain the different prevalences of CMV disease in UC and CD [8]. These findings could explain the fact that infliximab does not seem to affect CMV reactivation, as found in a prospective study in CD, supporting the safety of short-term treatment [10]. Similarly, D'Ovidio *et al.* [11] found that infliximab did not appear to induce progression from CMV infection to disease.

It remains to be determined whether IHC is the best diagnostic test to decide whether it is necessary to undergo a specific therapy or not, mostly because quantitative real-time PCR in inflamed mucosa has a better sensitivity to detect CMV, even if it can lead to false-positive results. After a systematic review, Ayre *et al.* [2] considered that only detection by histopathology seemed to be clinically relevant and appropriate for specific therapy with antiviral medications. Nevertheless, Yoshino *et al.* [12] concluded

that the use of quantitative real-time PCR for detecting CMV-DNA in inflamed mucosa was appropriate for the diagnosis and the consecutive treatment of CMV infection. So far, it is recommended in the current guidelines by the European Crohn's and Colitis Organization to use IHC or PCR as diagnostic tests for CMV colitis in IBD patients [13]. Our study showed that biopsy PCR was performed in seven patients and was always positive; this result is in agreement with the high sensitivity of the test.

For CMV therapy, in the literature, there is an ongoing debate in which cases a specific treatment is needed and which cases feature a spontaneous remission. Interestingly, a recent study found that IBD patients with a high density of viral inclusions in the biopsy sample benefit from antiviral therapy [14]. Roblin *et al.* [15] found a relationship between CMV DNA load in inflamed tissue and resistance to three successive treatments (steroids, infliximab and cyclosporine). A study suggested that the absence of large ulcers in patients with active UC and a positive mucosal viral assay are signs of a latent CMV infection, therefore not requiring an antiviral therapy. The authors suggested that large controlled trials are needed to confirm the usefulness of antiviral therapy in patients with deep colonic ulcers [16]. A randomized trial in adult solid organ transplant recipients with CMV disease showed that oral valganciclovir is not inferior to intravenous ganciclovir and has a comparable safety for the treatment of CMV disease [17]. European Crohn's and Colitis Organization guidelines recommend treatment with ganciclovir and an eventual switch to valganciclovir when CMV is detected in colon tissue, and consider that stopping of immunosuppressive therapy is necessary only in cases of systemic CMV reactivation [13].

As shown in other studies, we found a high proportion of patients who were treated with corticosteroids while suffering from CMV disease [3]. Interestingly, we found that all patients had received immunosuppressive therapy or were immunocompromised. The majority of patients received azathioprine, steroids and infliximab in combination.

Jacobson *et al.* [18] found a prevalence of gastrointestinal disease caused by CMV in 2.2% of AIDS patients. Santos *et al.* [19] analysed a cohort of lung transplant recipients and found that delayed-onset and early-onset CMV disease occurred in 13.7 and 3.3% of patients. CMV colitis is rare in UC patients without steroids or other immunomodulators as IBD therapy. CMV colitis in healthy individuals is extremely rare [2]. These results suggest that CMV disease needs some degree of immunosuppression to evolve, and that in IBD, both therapy and disease itself contribute towards CMV reactivation and disease.

Overall, the vast majority of CMV disease occurs in patients with UC rather than CD. Most patients who develop a CMV disease are treated with immunosuppressive medication. Testing for CMV disease should be performed in all patients who have a deteriorated course of IBD, especially in patients with severe and therapy-refractory IBD.

Our study has several strengths and limitations such as the selection of only one tertiary centre and use of a retrospective approach. However, our main strength is the lack of bias in the selection of the patients in their diagnosis of UC or CD and the extent of the disease. A limitation could be that it cannot clearly be excluded that CMV is a bystander and not the contributor towards the colitis in the cases presented. What speaks against this is that all IHC CMV-positive biopsies were obtained from inflamed mucosa and that in the three cases where biopsies were obtained from noninflamed mucosa, these were all IHC negative for CMV. Another limitation is that we did not have information on the disease course of the patients who did not have CMV colitis.

In conclusion, on the basis of the existing literature and on our data, it would be of interest to further investigate CMV disease and its treatment to confirm the results obtained so far.

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Conflicts of interest

There are no conflicts of interest.

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